REMARKS

Claims 3-13 are currently pending in the application. Only claims 3, 5, and 9 are in independent form.

Claims 3-4, 7-9, 10 and 13-16 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office Action states that while the specification is enabling for inhibiting the expression of tumor necrosis factor-alpha (TNF-α) *in vitro*, it does not reasonably provide enablement for modulating, which includes enhancing and inhibiting, the expression of TNF-α *in vivo*. In order to further prosecution, the claims have been amended to specifically recite only inhibiting the expression of TNF-α, thus overcoming a portion of the present rejection.

The Office Action also states that the specification as filed does not disclose a successful *in vivo* delivery of the antisense/ribozyme compounds and that such knowledge is not currently known in the art. The Office Action states that the current state of the art teaches that the behavior of antisense oligonucleotides *in vivo* and *in vitro* is unpredictable. However, as set forth in the attached paper written by Applicants, there is disclosed that the *in vivo* use of the method as set forth in the present application does perform as indicated in the *in vitro* studies. Specifically, the attached article shows data collected by the Applicants utilizing the methods of the present invention in rats. This study shows that rats treated with the methods and compositions of the present application developed the results that were predicted based upon the *in vitro* study. Accordingly, there is sufficient support for the specification as currently pending, and reconsideration of the rejection is respectfully requested.

Claims 5-6 and 9-12 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

The Office Action states that there are numerous phrases in these claims that are unclear as to how they relate to the other aspects of the claim. Accordingly, in order to further prosecution, the claims have been amended to more specifically cite both what is included in the antisense oligonucleotide and how this oligonucleotide results in the regulation of TNF-α expression. Reconsideration of the rejection is respectfully requested.

Claim 5 stands rejected under 35 U.S.C. § 102(e) as being anticipated by the Nyce, et al patent. Reconsideration of the rejection under 35 U.S.C. § 102(e), as anticipated by the Nyce, et al patent, as applied to the claims, is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

The Office Action states that claim 5 reads on a synthetic nuclease resistant antisense oligonucleotide for selectively inhibiting human TNF-α comprising an exon targeting sequence flanking donor splice sites. The Office Action states that the claim is interpreted as reading on synthetic antisense oligodeoxynucleotides targeting intron-exon borders of human TNF-α. However, while the Nyce, et al reference does disclose an adenosine A_1 that has an antisense molecule that may target the 5' or 3' intron-exon junctions of

the adenosine A_1 receptor, the patent strictly discloses the adenosine A_1 receptor. There is no mention of targeting intron-exon junctions for other genes such as TNF-α. Furthermore, this patent was filed prior to full characterization of adenosine A_1 receptor. At the time of the filing, delineation of the specific intron-exons was not completely understood. While targeting TNF-α is disclosed in column 3 of the patent, this is merely a laundry list of possible targets and there is no indication or suggestion in the specification as a whole for targeting TNF-α. Instead, all that is targeted is the A_1A receptor, and this targeting is very hypothetical. From the teachings of the Nyce et al patent, it could not be extrapolated that TNF-α also could be targeted using the information provided by the patent.

In a paper by Deckert, et al in 1995, there was disclosed further characterization of the adenosine A_1 receptor genes. Since there is no homology between TNF-α and the A_1A receptor gene, and there is no similarity in function between these two sequences, there is no indication that merely the knowledge pertaining to A_1A would be useful with regard to TNF-α. Accordingly, reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

This Preliminary Amendment is being filed to amend the application in response to the Final Office Action in the parent application from

which this application depends. Applicants wish to correct those issues currently outstanding from prosecution as it ended in the parent application.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Dated: September 23, 2002

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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Box CPA Application, Assistant Commissioner for Patents, Washington, DC 20231.

Connie Herty

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

5. (Twice Amended) A synthetic nuclease resistant antisense oligodeoxynucleotide for selectively inhibiting human tumor necrosis factor alpha, said antisense oligonucleotide comprising: an exon targeting an exon sequence [which] of TNF-α that [flanking] flanks at least one donor splice [sites] site, said targeting thereby [regulating] inhibiting expression of TNF-α.